

REMARKS

I. Background

The present Amendment is in response to the Office Action mailed September 8, 2008. Currently, claims 201, 205-208, 211, and 228 are amended, and claims 234-236 have been cancelled. Accordingly, claims 201-203, 205-209, 211, 213-214, 220, 221, 224-228, and 230-233 are now pending for the Examiner's consideration in light of the following remarks.¹

Applicant respectfully asserts that all claim amendments are supported by the specification as originally filed in by the patent applications to which the instant application claims priority. The amendments are supported by the instant patent application at paragraphs [0142, 0144-0145, 0248, 0258-0260, 0268-0269], Examples 7-8 and Figures 19-31. Similarly, the amendments are supported by 10/613,077 at paragraphs [0084-0087, 0204, 0215-0217, 0225-0226], Examples 7-8 and Figures 19-31. Thus, entry of the present amendments is respectfully requested because the amendments are supported by the instant patent application as well as the priority applications, and entry thereof does not introduce any new matter.

II. Priority

Applicant respectfully requests the correct priority to be acknowledged in the present application. At the time of the 371 nationalization of PCT patent application PCT/US2004/010343 on September 30, 2005, Applicant filed an Application Data Sheet (ADS) and a Preliminary Amendment, both of which identified the priority information for the instant patent application. A copy of the portion of the ADS and Preliminary Amendment identifying the priority information is pasted into this document herebelow.

In the ADS:

¹ Please note that the following remarks are not intended to be an exhaustive enumeration of the distinctions between any cited references and the claimed invention. Rather, the distinctions identified and discussed below are presented solely by way of example to illustrate some of the differences between the claimed invention and the cited references. In addition, Applicants request that the Examiner carefully review any references discussed to ensure that Applicants understanding and discussion of the references, if any, is consistent with the Examiner's understanding. If the Examiner's understanding of any of the references is not consistent with the Applicant's understanding of any of the references, Applicant respectfully requests the Examiner to provide specific citations within the individual references for support of the Examiner's understanding.

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Non-Provisional of	60/542,668	06 February 2004
This Application	Non-Provisional of	60/542,646	06 February 2004
This Application	Non-Provisional of	60/543,640	10 February 2004
This Application	Non-Provisional of	60/543,661	10 February 2004
This Application	Continuation-in-part of	10/406,908	02 April 2003
This Application	Continuation-in-part of	10/613,077	01 July 2003
This Application	National Stage of	PCT/US2004/010343	01 April 2004

In the Preliminary Amendment:

Priority

This application is a national stage application of PCT/US2004/010343, international filing date April 1, 2004, published in English as international publication number WO 2004/090105 A2 on October 21, 2004, which claims the benefit of the filing date of U.S. Provisional Patent Application Nos. 60/542668, filed February 6, 2004; 60/542646, filed February 6, 2004; 60/543640, filed February 10, 2004; and 60/543661, filed February 10, 2004; the international application is also a continuation-in-part of U.S. Patent Application Serial No. 10/406908, filed April 2, 2003, and U.S. Patent Application Serial No. 10/613,077, filed July 1, 2003.

Furthermore, PCT patent application PCT/US2004/010343 identifies on its face that it claims priority to U.S. Patent Applications: 10/406,908 filed 2 April 2003, 10/613,077 filed 1 July 2003, 60/542,668 filed 6 February 2004, 60/542,646 filed 6 February 2004, 60/543,640 filed 10 February 2004, and 60/543,661 filed 10 February 2004.

In view of the foregoing, the instant application has a claim of priority through PCT Patent Application PCT/US2004/010343 to U.S. Patent Applications: 10/406,908 filed 2 April 2003, 10/613,077 filed 1 July 2003, 60/542,668 filed 6 February 2004, 60/542,646 filed 6 February 2004, 60/543,640 filed 10 February 2004, and 60/543,661 filed 10 February 2004.

Accordingly, Applicant respectfully requests correction of the priority of the instant patent application.

III. Corrected Filing Receipt

Applicant respectfully requests a corrected filing receipt that identifies the full priority of the instant patent application to which it is entitled. The documents (e.g., ADS, Preliminary Amendment, and published PCT Patent Application PCT/US2004/010343 (WO 2004/090105)) filed on September 30, 2005 at the time of the 371 nationalization of PCT/US2004/010343 provide sufficient evidence to the claim of priority.

IV. Claim Objections

The Office Action has objected to claims 206, 207, 228, and 230-233 due to informalities. Applicant has amended claim 206 (claim 207 depends from claim 206) to clarify that the “at least one nucleotide” has the 2’ modification. Additionally, Applicant has amended claim 228 (claims 230-233 depend from claim 228) in accordance with the suggestion provided in the Office Action. Thus, Applicant respectfully requests withdrawal of the objection to claims 206, 207, 228, and 230-233.

V. Rejections Under 35 U.S.C. § 112, First Paragraph

The Office Action rejects claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-236 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action alleges that the limitation of the antisense region being “at least substantially complementary with the mRNA of the target gene” is new matter and was introduced into the claims filed on 11/10/06 and is not supported by the instant specification. Applicant respectfully disagrees and directs attention to U.S. Patent Application 10/613,077², filed July 1, 2003, from which this instant patent application claims priority, paragraphs [0084-0087], and [0204]. Essentially the same paragraphs and information contained therein are included in the instant patent application³ at paragraphs [0142], [0144-0145], and [0248]. While the exact phrase “at least substantially complementary with the mRNA of the target gene” is not specifically recited, the information contained in the identified paragraphs is sufficient to satisfy the written description requirement because there is not a “verbatim” requirement in U.S. patent applications. Thus, the identified paragraphs provide sufficient written description support for

² U.S. Patent Application 10/613,077 has been published with Pre-grant Publication Number 2004/0266707, and all paragraph references refer to the published application.

³ The instant U.S. Patent Application has been published with Pre-grant Publication Number 2007/0167384, and all paragraph references refer to the published application.

the claim limitation of an antisense strand being “at least substantially complementary with the mRNA of the target gene.”

Applicant has cancelled claims 234-236.

Thus, Applicant respectfully requests withdrawal of the rejection to claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-233 under 35 U.S.C. 112, first paragraph.

VI. Rejection Under 35 U.S.C. § 102

The Office Action rejects claims 201, 202, 206, 207, 213, 220, 221, 228, 231, and 234-236 under 35 U.S.C. § 102(b) as being anticipated by Giese et al. (PG-PUB 2004/0180351). Applicant respectfully traverses the rejection because the Office Action has not established that Giese teaches each and every element of the presently claimed invention.

In accordance with Applicant’s understanding, Giese teaches siRNA for silencing a target gene, wherein the siRNA include a first strand (e.g., antisense strand of present invention) that is at least partially complementary to a target nucleic acid and a second strand (e.g., sense strand of the present invention) that is at least partially identical to the target nucleic acid. In Figure 1, the top strand is defined to be the first strand (e.g., antisense strand) and the bottom strand is defined to be the second strand (e.g., sense strand). Therefore, the illustrations of siRNA in Giese are the opposite compared to the illustrations provided in the present patent application, where the present patent application identifies the top strand to be a sense strand and the bottom strand to be the antisense strand that has at least substantial complementarity with the target nucleic acid. As such, the figures in Giese need to be analyzed by identifying the top strand to be comparable to the antisense strand of the present application (see paragraph [0064]).

In view of the reverse orientation of the siRNA of Giese, Figures 2A-2B of Giese do not show the first and second nucleotides from the 5’ end of the sense strand (e.g., bottom strand) having 2’ modifications. While various modification patterns are shown in the figures, none of the figures shows the first and second nucleotides from the 5’ end of the sense strand (e.g., bottom strand) having 2’ modifications with the rest of the sense nucleotides other than the first and second nucleotides each include a 2’-OH. Additionally, Giese states that the 5’-hydroxy group of the second strand (i.e., sense strand) is unmodified (paragraph [0096]). Also, Giese defines an “end modification” as only the terminal nucleotide of a 3’ or 5’ end being modified, and thereby Giese does not teach that an end modification includes both the first and second nucleotides from a 5’ end being modified (paragraphs [0096-0103]). Accordingly, an “end

modification” of Giese only includes the terminal nucleotide, but not the penultimate nucleotide. This is further supported by paragraph [0123] which teaches that it is preferable that the penultimate nucleotide is unmodified or the beginning of an unmodified stretch of nucleotides in the second strand (i.e., sense strand).

In view of the foregoing, Applicant respectfully asserts that Giese does not anticipate the presently claimed invention because it does not teach “a substantially non-functional sense strand comprising: a first nucleotide of the sense strand closest to the 5’ end of the sense strand having a 2’-O-alkyl modification; and a second nucleotide of the sense strand next closest to the 5’ end of the sense strand having a 2’-O-alkyl modification, wherein the rest of the sense nucleotides other than the first and second nucleotides each include a 2’-OH,” as recited in claim 201 and similarly recited in claim 228. Since Giese does not teach each and every element of the presently pending claims, Giese does not anticipate the presently claimed invention. Thus, Applicant respectfully requests withdrawal of the rejection to claims 201, 202, 206, 207, 213, 220, 221, 228, 230, and 231 under 35 U.S.C. § 102(b).

VII. Rejection Under 35 U.S.C. § 103

The Office Action rejects claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-233 under 35 U.S.C. § 103(a) as being unpatentable over Giese et al. (PG-PUB 2004/0180351) in view of Vargeese et al. (PG-PUB 2004/0110296). Applicant respectfully traverses because the Office Action has not established a *prima facie* case of obviousness.

In addition to the foregoing comments regarding Giese, Applicant also interprets Giese to teach that the sense strand include internal modifications when the sense strand is modified. Figures 2A-2C, 10C, 11C, 12B, 15A-15B, 16A-16C, all show the sense strand to have internal modifications when the sense strand is modified, and none of the illustrated sense strand include a “sense strand comprising: a first nucleotide of the sense strand closest to the 5’ end of the sense strand having a 2’-O-alkyl modification; and a second nucleotide of the sense strand next closest to the 5’ end of the sense strand having a 2’-O-alkyl modification, wherein the rest of the sense nucleotides other than the first and second nucleotides each include a 2’-OH,” as recited in claim 201 and similarly recited in claim 228. While Giese may illustrate various modification patterns, no valid reason is provided by Giese to only modify the first and second nucleotides of the 5’ end of the sense strand.

In accordance with Applicant's understanding, Vargeese is combined with Giese because Vargeese teaches cholesterol as a conjugate to siRNA. However, Vargeese does not cure the deficiencies of Giese, and thereby does not teach or suggest "sense strand comprising: a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification, wherein the rest of the sense nucleotides other than the first and second nucleotides each include a 2'-OH," as recited in claim 201 and similarly recited in claim 228.

In view of the foregoing, Applicant respectfully asserts that the combination of Giese and Vargeese does not teach or suggest each and every element of the presently claimed invention because the combination does not teach or suggest "a substantially non-functional sense strand comprising: a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification, wherein the rest of the sense nucleotides other than the first and second nucleotides each include a 2'-OH," as recited in claim 201 and similarly recited in claim 228. Nothing in Giese nor Vargeese provides motivation or a valid reason to a skilled artisan to modify teachings therein singly or in combination to make the claimed invention.

Additionally, Giese teaches away from a sense strand having a modification at the penultimate nucleotide (paragraph [0123]), which is the second nucleotide from the 5' end. Giese actually states, "In a preferred embodiment the second (penultimate) nucleotide at the terminus of the strand and stretch, respectively, is an unmodified nucleotide or the beginning of group of unmodified nucleotides." Giese goes on in the same paragraph to state, "In a further preferred embodiment, the unmodified nucleotide or unmodified group of nucleotide is located at the 5'-end of the first strand and first stretch." Under the terminology of Giese the second strand is the sense strand. Thus, Giese teaches away from the presently claimed invention, and since Vargeese does not correct the deficiencies of Giese, the combination of references teaches away from the presently claimed invention.

Applicant respectfully asserts that neither Giese nor Vargeese or the combination thereof provides any valid reason to modify siRNA in order to arrive at the presently claimed invention. Firstly, neither Giese nor Vargeese teach or suggest the claimed modification pattern because the

sense strand is shown to have modifications other than those presently claimed. Secondly, Giese teaches away from the presently claimed modification pattern in paragraph [0123]). Thirdly, any routine optimization under Giese would necessarily follow the teachings of Giese which teach additional modifications to nucleotides of the sense strand other than the first and second nucleotides from the 5' end, and thereby routine optimization of the modifications of Giese would not lead to the modification that is presently claimed. Thus, there is no valid reason to modify the teachings of Giese, Vargeese, or the combination thereof in order to arrive at the presently claimed invention.

Since the combination of Giese and Vargeese does not teach or suggest each and every element of the presently claimed invention, and teaches away from the presently claimed invention, a *prima facie* case of obviousness has not been established for independent claims 201 and 228. Claims 202, 206, 207, 213, 220, 221, 224-227, and 230-233 depend from claim 201 or claim 228, and thereby are allowable for the same reasons claims 201 and 228 are allowable. Thus, Applicant respectfully requests withdrawal of the rejection to claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-233 under 35 U.S.C. § 103(a).

VIII. Rejection Under 35 U.S.C. § 103

The Office Action rejects claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-233 under 35 U.S.C. § 103(a) as being unpatentable over Giese et al. (PG-PUB 2004/0180351) in view of Vargeese et al. (PG-PUB 2004/0110296 in further view of Fire et al. (U.S. 6,506,559). Applicant respectfully traverses because the Office Action has not established a *prima facie* case of obviousness.

In accordance with Applicant's understanding, Fire is combined with Giese and Vargeese because Fire teaches methods of inhibiting expression of a target gene in a cell by using double stranded siRNA. Fire However, Fire does not cure the deficiencies of the combination of Giese and Vargeese recited above, and thereby Fire and/or the combination of references does not teach or suggest "sense strand comprising: a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification, wherein the rest of the sense nucleotides other than the first and second nucleotides each include a 2'-OH," as recited in claim 201 and similarly recited in claim 228.

Additionally, Fire does not correct or change the teachings of Giese and/or Vargeese with respect to teaching away from the present invention, and thereby the combination of Giese, Vargeese, and Fire teach away from the present invention for the same reasons discussed above.

Furthermore, Fire does not include any teachings or suggestions in order to provide a valid reason to change the teachings of Giese and/or Vargeese in order to arrive at the presently claimed invention. That is, the combination of Giese, Vargeese, and Fire does not provide a valid reason for changing the teachings of Giese or the combination in order to arrive at the presently claimed invention for the same reasons that the combination of Giese and Vargeese does not provide any valid reason to modify the teachings thereof.

Since the combination of Giese, Vargeese, and Fire does not teach or suggest each and every element of the presently claimed invention, and teaches away from the presently claimed invention, a *prima facie* case of obviousness has not been established for independent claims 201 and 228. Claims 202, 206, 207, 213, 220, 221, 224-227, and 230-233 depend from claim 201 or claim 228, and thereby are allowable for the same reasons claims 201 and 228 are allowable. Thus, Applicant respectfully requests withdrawal of the rejection to claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-233 under 35 U.S.C. § 103(a).

IX. Double Patenting

The Office Action provisionally rejects claims 201 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6, and 7 of co-pending Application No. 11/825,461. Additionally, Office Action provisionally rejects claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-236 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33 of co-pending Application No. 11/619,993. A terminal disclaimer is filed herewith with respect to Application No. 11/825,461 and Application No. 11/619,993.

SUMMARY

In view of the foregoing, Applicant respectfully submits that the other rejections to the claims are now moot and do not, therefore, need to be addressed individually at this time. It will be appreciated, however, that this should not be construed as Applicant acquiescing to any of the purported teachings or assertions made in the last action regarding the cited art or the pending application, including any official notice. Instead, Applicant reserves the right to challenge any of the purported teachings or assertions made in the last action at any appropriate time in the

future, should the need arise. Furthermore, to the extent that the Examiner has relied on any Official Notice, explicitly or implicitly, Applicant specifically requests that the Examiner provide references supporting the teachings officially noticed, as well as the required motivation or suggestion to combine the relied upon notice with the other art of record.

Applicant believes claims 201-203, 205-209, 211, 213-214, 220, 221, 224, 228, and 230-233 are in allowable form as discussed above. Thus, Applicant respectfully requests reconsideration of the application and allowance of presently pending claims.

The Commissioner is hereby authorized to charge payment of any of the following fees that may be applicable to this communication, or credit any overpayment, to **Deposit Account No. 23-3178**: (1) any filing fees required under 37 CFR § 1.16; (2) any patent application and reexamination processing fees under 37 CFR § 1.17; and/or (3) any post issuance fees under 37 CFR § 1.20. In addition, if any additional extension of time is required, which has not otherwise been requested, please consider this a petition therefore and charge any additional fees that may be required to **Deposit Account No. 23-3178**.

In the event that the Examiner finds remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, the Examiner is requested to contact the undersigned attorney by telephone at (801) 533-9800.

Dated this 8th day of January, 2009.

Respectfully submitted,

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